# Asymmetry of cortical decline in subtypes of primary progressive aphasia

Emily Rogalski, PhD
Derin Cobia, PhD
Adam Martersteck, BS
Alfred Rademaker, PhD
Christina Wieneke, BA
Sandra Weintraub, PhD
M.-Marsel Mesulam, MD

Correspondence to
Dr. Rogalski:
erogalski@gmail.com

## ABSTRACT

**Objective:** The aim of this study was to provide quantitative measures of changes in cortical atrophy over a 2-year period associated with 3 subtypes of primary progressive aphasia (PPA) using whole-brain vertex-wise and region-of-interest (ROI) neuroimaging methods. The purpose was to quantitate disease progression, establish an empirical basis for clinical expectations, and provide outcome measures for therapeutic trials.

**Methods:** Changes in cortical thickness and volume loss as well as neuropsychological performance were assessed at baseline and 2-year follow-up in 26 patients who fulfilled criteria for logopenic (8 patients), agrammatic (10 patients), and semantic (8 patients) PPA subtypes. Whole-brain vertex-wise and ROI imaging analysis were conducted using the FreeSurfer longitudinal pipeline.

**Results:** Clinical deficits and cortical atrophy patterns showed distinct patterns of change among the subtypes over 2 years. Results confirmed that progression for each of the 3 subtypes showed left greater than right hemisphere asymmetry. An ROI analysis also revealed that progression was greater within, rather than outside, the language network.

**Conclusions:** Preferential neurodegeneration of the left hemisphere language network is a common denominator for all 3 PPA subtypes, even as the disease progresses. Using a focal cortical language network ROI as an outcome measure of disease progression appears to be more sensitive than whole-brain or ventricular volume measures of change and may be helpful for designing future clinical trials in PPA. *Neurology*® 2014;83:1184–1191

## GLOSSARY

**ANOVA** = analysis of variance; **eTIV** = estimated total intracranial volume; **IFG** = inferior frontal gyrus; **LH** = left hemisphere; **PPA** = primary progressive aphasia; **PPA-G** = primary progressive aphasia–agrammatic; **PPA-L** = primary progressive aphasia–logopenic; **PPA-S** = primary progressive aphasia–semantic; **PSTC** = perisylvian temporal cortex; **RH** = right hemisphere; **ROI** = region of interest; **V1** = visit 1; **V2** = visit 2; **WAB-AQ** = Western Aphasia Battery–Aphasia Quotient.

Primary progressive aphasia (PPA) is a clinical dementia syndrome defined by deterioration of language functions over time and relative sparing of other cognitive domains.[1] Three clinical variants are based on the nature of language impairment: agrammatic (PPA-G), semantic (PPA-S), and logopenic (PPA-L).[2,3] Great strides have been made to understand the relationship among clinical phenotype, regions of peak atrophy, and underlying neuropathology; however, quantitative information about the clinico-anatomical course of the syndrome remains relatively sparse. Descriptive case reports[1] and small group studies have established the focal nature of PPA over time, but few studies[4,5] make comparisons among the 3 PPA subtypes and provide quantitative estimates that may be useful for designing therapeutic trials.

The current study provides quantitative metrics of cortical change associated with PPA subtypes over a 2-year interval using whole-brain vertex-wise and region-of-interest (ROI) measures to determine the distribution and asymmetry of atrophy for each. Of particular interest was determining whether progressive atrophy was greater within, vs outside of, the language network.

## METHODS

**Participants.** The core diagnosis of PPA was based on an initially isolated and progressive language impairment.[1,6,7] Thirty-one patients had a root diagnosis of PPA and longitudinal data available at the time of analysis. Five were excluded from the

Supplemental data at Neurology.org

From the Cognitive Neurology and Alzheimer's Disease Center (E.R., A.M., C.W., S.W., M.-M.M.), and Departments of Psychiatry and Behavioral Sciences (D.C., S.W.), Preventative Medicine (A.R.), and Neurology (M.-M.M.), Northwestern University Feinberg School of Medicine, Chicago, IL.

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analysis: 2 too severely impaired at their baseline visit to be subtyped (Western Aphasia Battery–Aphasia Quotient [WAB-AQ] <65), 2 with a mixed phenotype, and one who was unclassifiable. Thus, 26 patients with early to moderate PPA at their baseline visit (based on WAB-AQ and clinical assessment) and 35 cognitively healthy controls of similar age and education level were included in the study. All patients with PPA completed MRI at visit 1 (V1) and visit 2 (V2; 2 years later; range: 21–27 months).

**Standard protocol approvals, registrations, and patient consents.** Participants were recruited from Northwestern University's PPA Research Program. Written informed consent was obtained from all participants. The Northwestern University Institutional Review Board approved this study.

**Subtyping.** Subtyping was determined at the initial visit by quantitative performance on the measures described below according to previously reported guidelines[3,8] and clinical judgment when data were not available. This study included 8 PPA-L, 10 PPA-G, and 8 PPA-S patients. One of the patients with PPA-S previously reported[8] was in the "prodromal" stage at V1.

**Neuropsychological measures.** ***Aphasia severity.*** The WAB-AQ[9] measured aphasia severity based on auditory comprehension, naming, repetition, and spontaneous speech.

***Grammatical production.*** A composite score for grammatical processing was created from 15 noncanonical sentence items from the Northwestern Anagram Test[10] and 15 noncanonical sentence items from the Sentence Production Priming Test of the Northwestern Assessment of Verbs and Sentences, as described previously.[8]

***Semantic processing.*** A subset of moderately difficult items (items 157–192) from the fourth edition of the Peabody Picture Vocabulary Test[11] was used as a measure of auditory lexical-semantic processing. These items were specifically chosen because of their proven value in subtyping PPA.[3]

***Naming.*** Naming ability was assessed with the Boston Naming Test.

***Repetition.*** The 6 most difficult items (items 10–15) from the WAB Repetition subtest were used to quantitate repetition, as previously described.[8]

***Nonlanguage domains.*** The presence of deficits in memory performance, comportment, and/or visuospatial abilities would preclude a PPA diagnosis at baseline. These features were judged on the basis of formal test scores and/or informant report by an expert behavioral neurologist (M.-M.M.) and deemed to be intact at V1. Motor-speech impairments were absent in the patients with PPA-S and PPA-L and present in 4 patients with PPA-G at V1.

**MRI acquisition parameters.** T1-weighted, 3-dimensional, magnetization-prepared rapid-acquisition gradient echo sequences (repetition time = 2,300 milliseconds, echo time = 2.91 milliseconds, inversion time = 900 milliseconds, flip angle = 9°, field of view = 256 mm), recording 176 slices at a slice thickness of 1.0 mm, were acquired on a 3T Siemens TRIO (Siemens AG, Erlangen, Germany) using a 12-channel birdcage head coil. Imaging was performed at Northwestern University's Center for Translational Imaging.

**Cortical thickness and volume measurements.** MRIs were processed using the cross-sectional[12] and longitudinal[13] pipelines from FreeSurfer (v5.1.0, http://surfer.nmr.mgh.harvard.edu/). Cortical thickness estimates were calculated by measuring surface distances between representations of the white-gray and pial-CSF boundaries. Topological surface errors were corrected by manual intervention according to established guidelines[14] in an iterative fashion until completely resolved.

In addition to whole-brain vertex-wise cortical thickness analysis, 3 bilateral a priori ROIs were identified. First, an ROI of the entire neocortical surface (cortex) served as a global measure of atrophy for each hemisphere.[15] Second, a language network ROI was defined for the perisylvian cortex, including the insula and surrounding temporal regions (perisylvian temporal cortex [PSTC]). This ROI was defined in magnetic resonance space under the guidance of an expert neuroanatomist (M.G.) using anatomical descriptions from Duvernoy[16] and Naidich et al.[17] Boundaries are as follows: starting at the anterior portion of inferior frontal sulcus, the boundary moves posteriorly to the precentral sulcus, then ventrally to upper limits of the insula and posteriorly to the descending limb of the postcentral sulcus, superiorly along the postcentral sulcus, and dorsally along the intraparietal sulcus to its descending termination point. The boundary then takes the shortest distance to the temporal/occipital notch, and proceeds anteriorly along the transverse collateral sulcus into the collateral sulcus, and then to the rhinal sulcus, continuing dorsally into the falciform fold of the insulo-temporal junction, anteriorly into the lateral orbital sulcus, and finally takes the shortest path back into the anterior portion of inferior frontal sulcus. Demarcation of this region showed good inter- and intrarater reliability in a test set of 10 subjects manually traced by E.R. and D.C.[18] Dynamic programming[19] delineated PSTC boundaries on a surface of the white-gray boundary, then propagated onto node-matched pial surface vertices. Finally, the PSTC ROI was generated across all study subjects as a cortical label using automated FreeSurfer algorithms. The third ROI consisted of cortical surface outside of the PSTC (remainder = cortex − PSTC) and served to determine whether changes in volume were occurring within or outside of the language network.

Estimates of cortical gray matter volume ($mm^3$) were extracted bilaterally for each ROI using standard FreeSurfer algorithms in subject native space. Adjustments for intracranial volume were calculated for ROI at each time point using validated methods within the FreeSurfer toolkit.[20] Because the data were longitudinal, each subject's estimated total intracranial volume (eTIV) was calculated based on the combined template from V1 and V2.[13] Normalized volume for each ROI was calculated using the following formula[20]:

$$\mathrm{ROI}_{\mathrm{normalized}} = \mathrm{ROI}_{\mathrm{native}} - \mathrm{ASF}\left(\mathrm{eTIV}_{\mathrm{native}} - \mathrm{eTIV}_{\mathrm{group}}\right),$$

where $\mathrm{ROI}_{\mathrm{normalized}}$ is the adjusted volume, $\mathrm{ROI}_{\mathrm{native}}$ is the FreeSurfer calculated ROI volume in patient native space, and $\mathrm{eTIV}_{\mathrm{native}}$ is for that patient and $\mathrm{eTIV}_{\mathrm{group}}$ is the average for the PPA group (1,514,132 $mm^3$). The Atlas Scaling Factor (ASF) is the ratio of volume expansion or contraction each MR volume undergoes during spatial normalization to FreeSurfer's average template.

The percent change in volume from V1 to V2 was calculated as follows:

$$\text{Percent Change} = \frac{\mathrm{V2} \times \mathrm{ROI}_{\mathrm{normalized}} - \mathrm{V1} \times \mathrm{ROI}_{\mathrm{normalized}}}{\mathrm{V1} \times \mathrm{ROI}_{\mathrm{normalized}}}$$

**Statistical analysis.** Vertex-wise cortical thickness between-group differences were calculated by conducting a general linear model across every vertex along the cortical surface, derived from structural magnetic resonance data processed with FreeSurfer. Within-group longitudinal vertex-wise analyses were conducted using paired *t* tests along the cortical surface. False discovery rates were set at 0.05 for these analyses.[21]

Paired *t* tests were used to compare ROI data from V1 to V2 within subtype with a Bonferroni-corrected significance criterion of $p \leq 0.017$. One-way analyses of variance (ANOVAs) and post hoc

**Table 1** Demographic information

| | PPA-L | PPA-G | PPA-S | NC |
|---|---|---|---|---|
| No. | 8 | 10 | 8 | 35 |
| Age at visit 1, y | 65.9 (7.1) | 65.5 (7.0) | 59.2 (4.1) | 62.4 (7.0) |
| Sex, % male | 37.5 | 50 | 37.5 | 48.6 |
| Education, y | 16.6 (1.2) | 16.4 (2.8) | 16.6 (3.0) | 16 (2.4) |
| Symptom duration, y | 5.1 (2.1) | 5.3 (1.4) | 5.3 (1.3) | — |
| Months between visits | 24.4 (1.2) | 24.3 (1.1) | 24.0 (1.3) | — |

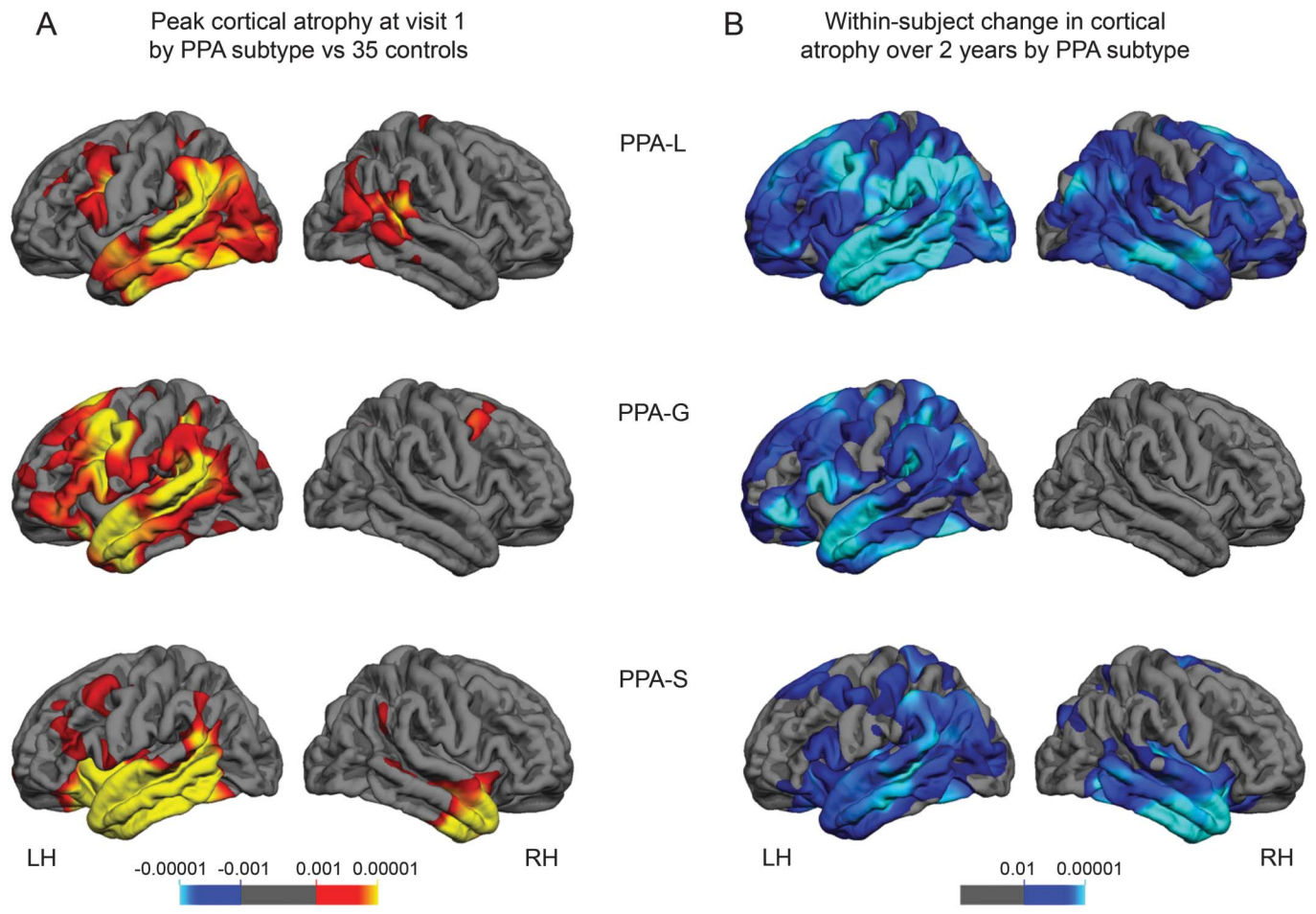
Abbreviations: NC = normal controls; PPA-G = primary progressive aphasia–agrammatic; PPA-L = primary progressive aphasia–logopenic; PPA-S = primary progressive aphasia–semantic.
Numbers are provided as means (SDs). There were no significant differences in demographics among the groups.

$t$ tests were used to compare subtypes. A significance criterion of $p \leq 0.05$ was used for the main effect and $p \leq 0.017$ was used for each of the 3 pairwise tests. Separate analyses were done for each ROI.

**RESULTS** Twenty-six patients with PPA (8 PPA-L, 10 PPA-G, 8 PPA-S) and 35 controls were included in the analyses. There were no significant differences in demographics among the groups (table 1).

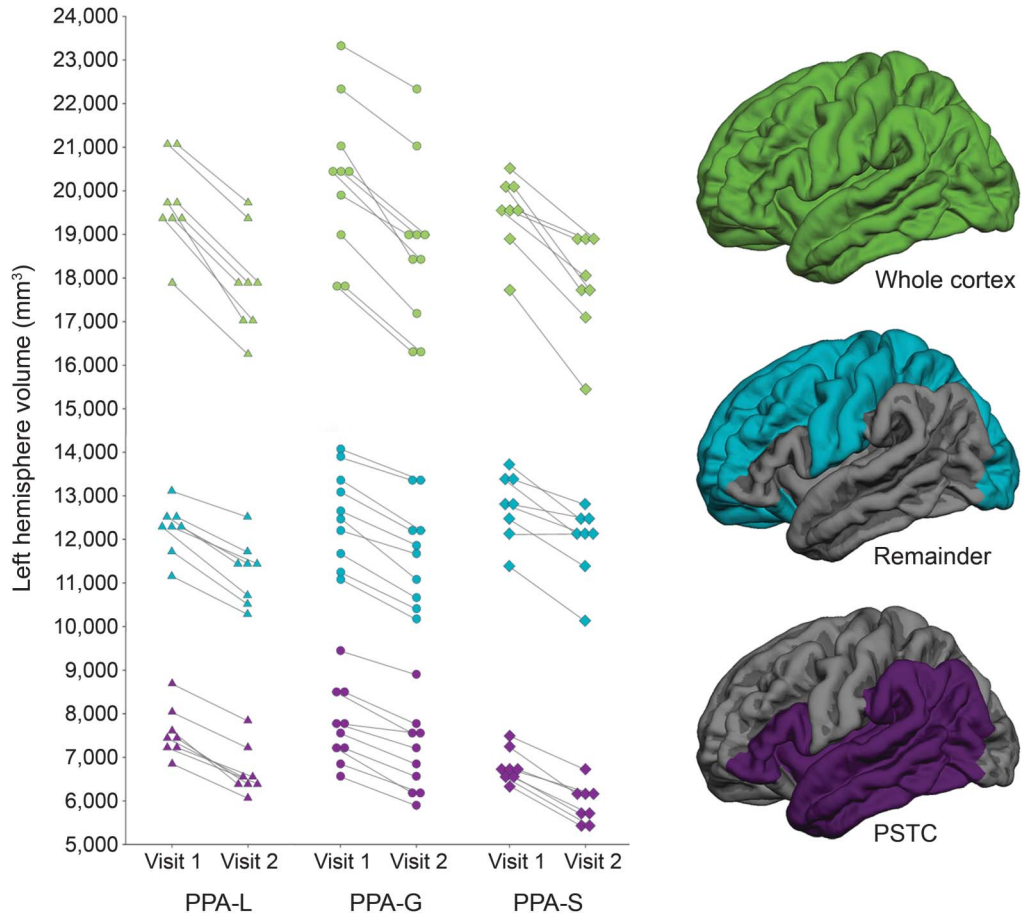
**Vertex-wise patterns of cortical atrophy by PPA subtype.** To identify regions of peak atrophy at V1 for each PPA subtype, vertex-wise thickness analyses across the entire cerebral cortex were used to compare each PPA subtype with the cognitively healthy controls. At V1, each PPA subtype showed asymmetrically greater atrophy in the left hemisphere (LH) (figure 1A, video on the *Neurology*® Web site at Neurology.org), consistent with previous reports.[3] Compared with controls, peak atrophy in the PPA-L group included the temporoparietal junction, as well as the superior middle and inferior temporal gyri of the LH with relative sparing of the anterior aspects of the temporal pole. LH atrophy was also present in the posterior portion of the inferior frontal gyrus (IFG) and the caudal middle frontal gyrus. The peak atrophy for the right hemisphere (RH) of the PPA-L group was minimal and included the posterior superior temporal gyrus, supramarginal gyrus, and inferior

**Figure 1** Atrophy patterns by PPA subtype




False discovery rate was set at 0.05 for each comparison. (A) Significant cortical thinning patterns for each PPA subtype at baseline compared with controls (red/yellow shading). (B) Significant within-subject cortical thinning patterns over 2 years for each PPA subtype (blue/green shading). The $p$ values are provided above each color bar. LH = left hemisphere; PPA = primary progressive aphasia; PPA-G = PPA-agrammatic; PPA-L = PPA-logopenic; PPA-S = PPA-semantic; RH = right hemisphere.

**Figure 2** Individual left hemisphere ROI volumes by visit



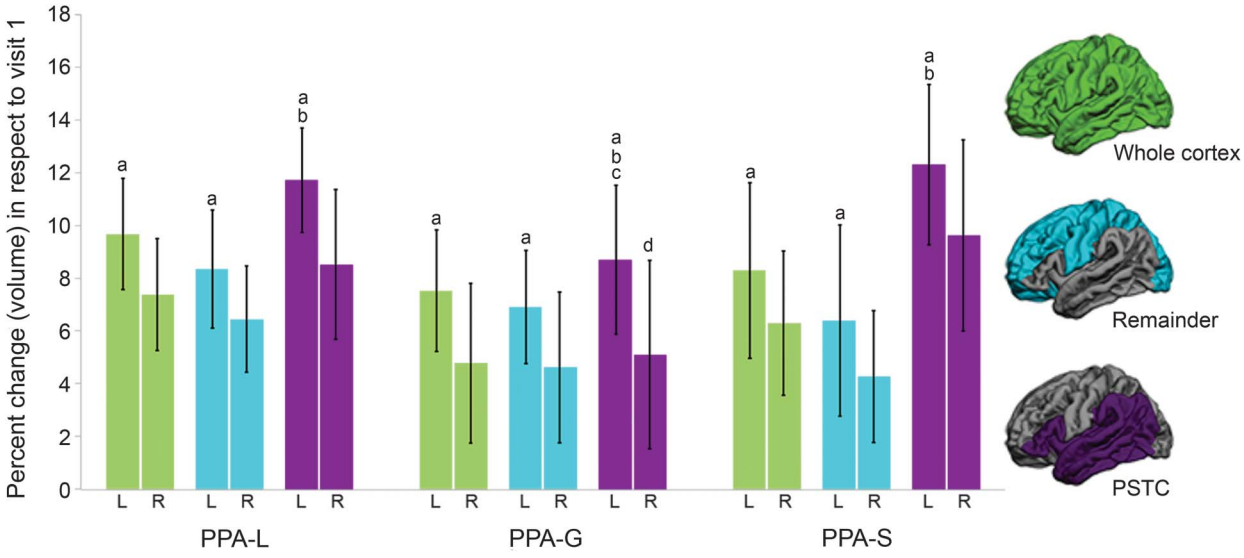

PPA-G = primary progressive aphasia–agrammatic; PPA-L = primary progressive aphasia–logopenic; PPA-S = primary progressive aphasia–semantic; PSTC = perisylvian temporal cortex; ROI = region of interest.

parietal regions. The PPA-G group showed atrophy throughout the perisylvian cortex compared with controls, including peak atrophy in IFG, caudal middle frontal gyrus, and in the temporal lobe involving the entire superior and middle temporal gyrus and the anterior portion of the inferior temporal gyrus. The RH for the PPA-G group was relatively spared. Compared with controls, the PPA-S group showed atrophy largely confined to the temporal lobe including the superior, middle, and inferior temporal gyri and the fusiform gyrus. The peak atrophy in the RH was most severe in the most anterior third of the temporal lobe.

Within-group, vertex-wise paired *t* tests were used to identify atrophy progression patterns from V1 to V2 for each PPA subtype (figure 1B, video). The distribution of the change in atrophy was greater in the LH than the RH for each subtype over the course of 2 years; however, each subtype showed a distinct pattern of atrophy. The within-group change for the PPA-L group was widespread encompassing nearly the entire cerebral cortex. The LH temporal lobe and temporoparietal junction regions showed more severe change than the IFG. Atrophy in the RH was greatest in the homologs of the LH perisylvian regions but also extended beyond these cortical regions. Significant vertex-wise change in atrophy within the PPA-G group was restricted to the LH and included the perisylvian cortex, anterior temporal regions, as well as frontal and parietal atrophy. The peak within-group change in atrophy for the PPA-S group was the most circumscribed of the 3 subtypes and included peak bilateral temporal atrophy, although the LH atrophy extended more posteriorly than the RH atrophy and included the temporoparietal region.

**Volume-based ROI analyses.** ***General ROI volume characteristics at each visit by subtype.*** LH ROI volumes for each participant are provided in figure 2. On average, the LH PSTC volume was smallest in the PPA-S group and reached significance in post hoc comparisons with the PPA-L and PPA-G groups at both V1 and V2 ($p \leq 0.011$, for each comparison; table e-1 on the *Neurology*® Web site at Neurology.org). There was no significant difference among the PPA subtypes' RH

**Figure 3** Percent change of cortical volume loss over 2 years by hemisphere and PPA subtype




[a] Within each subtype and for each ROI the rate of change was significantly greater in the left hemisphere than in the right hemisphere. [b] Percent change was significantly higher in the PSTC than the remainder ROI for the left hemisphere for each subtype. [c] The left hemisphere PSTC ROI of the PPA-G group showed a significantly smaller percent change in volume than PPA-L and PPA-S groups. [d] The right hemisphere PSTC ROI of the PPA-G group showed a significantly smaller percent change in volume than the PPA-S group. Bars represent SDs. L = left hemisphere; PPA = primary progressive aphasia; PPA-G = PPA-agrammatic; PPA-L = PPA-logopenic; PPA-S = PPA-semantic; PSTC = perisylvian temporal cortex; R = right hemisphere; ROI = region of interest.

PSTC volume at baseline or follow-up. Likewise, there were no significant differences among the subtypes for the cortex ROI volumes at V1 or V2 in either hemisphere. There were no significant differences among the subtypes for the remainder ROI volumes at V1 in either hemisphere. At V2, the only significant difference was in the RH remainder ROI volume, which was larger in the PPA-S group than the PPA-L group ($p = 0.013$).

As expected, there was decline in volume for each ROI and for each subtype from V1 to V2 for both the LH and RH ($p \leq 0.0013$, for each comparison; table e-1). LH volume of each ROI at each visit by participant is provided in figure 2.

***Characterization of the progression of atrophy over time.*** Percent change in ROI volume was examined for each hemisphere and subtype to determine whether progression was (1) asymmetric, (2) greater within or outside of the language network, and (3) had different rates among subtypes.

Paired *t* tests revealed that within each subtype and for each ROI, the percent change in volume was greater in the LH than the RH ($p \leq 0.009$, for each comparison; figure 3), which is consistent with the vertex-wise cortical thinning patterns observed in figure 1.

To determine whether the greatest declines were occurring within or outside of the LH language network, percent change in volume of the LH PSTC and remainder regions was compared (figure 3). The percent change was greater in the LH PSTC than the remainder ROI for each subtype ($p \leq 0.013$, for each comparison).

ANOVAs determined whether the percent change in volume of each ROI differed by subtype (figure 3). There was a main effect of the percent change in volume of the PSTC ROI for each hemisphere among the subtypes ($p \leq 0.021$, for each comparison). Post hoc analyses showed that the PSTC ROI of the PPA-G group had a smaller percent change in volume than the LH of the PPA-L group ($p = 0.014$) and both the LH and RH of the PPA-S group (LH: $p = 0.017$; RH: $p = 0.014$). There was no significant main effect when the percent change in volume of either the cortex or remainder ROI was compared among the subtypes for both the LH and RH.

**Sample size considerations.** Sample size calculations for small (25%) and medium (40%) effect sizes were based on the percent change in volume from the LH cortex and PSTC ROI for the PPA group and by subtype. Sample sizes were estimated both with and without a 35% inflation rate for attrition.[5] When the cortex was the outcome measure, 25 subjects with PPA were required for a small effect size and 10 for a medium effect size. When considering a 35% attrition rate, the required sample sizes increased to 34 and 14, respectively. Fewer subjects were required when the PSTC was the outcome measure: small effect size, 21 subjects with PPA; medium effect size, 8. When considering a 35% attrition rate, the required sample sizes increased to 29 and 11, respectively. Sample sizes were also estimated by subtype for each ROI (cortex —PPA-L: 12 small, 5 medium; PPA-G: 24 small, 10 medium; PPA-S: 20 small, 16 medium;

**Table 2** Average neuropsychological performance at baseline and 2-year follow-up by PPA subtype

| Neuropsychological test | PPA-L | PPA-G | PPA-S |
|---|---|---|---|
| **WAB-AQ** | | | |
| V1 | 91.7 (5.0) | 84.9 (7.9) | 84.5 (9.3) |
| V2 | 77.4 (14.9) | 51.4 (24.5)[a] | 69.4 (13.8) |
| **BNT** | | | |
| V1 | 91.9 (5.3) | 81.8 (16.3) | 20.0 (20.8)[b] |
| V2 | 63.1 (28.2) | 47.9 (35.3) | 7.9 (7.3)[b] |
| **PPVT** | | | |
| V1 | 97.2 (2.8) | 95.0 (4.3) | 52.1 (26.0)[b] |
| V2 | 87.2 (22.2) | 76.4 (17.8) | 42.2 (25.5)[b] |
| **Grammatical production** | | | |
| V1 | 85.0 (15.6) | 53.7 (28.1)[c] | 95.0 (11.5) |
| V2 | 60.6 (12.4) | 33.9 (15.0)[c] | 79.4 (17.1) |
| **WAB repetition (items 10–15)** | | | |
| V1 | 83.0 (9.5) | 72.3 (19.1)[d] | 92.6 (7.9) |
| V2 | 59.7 (15.5) | 30.3 (26.3)[e] | 72.5 (17.8) |

Abbreviations: BNT = Boston Naming Test; PPA = primary progressive aphasia; PPA-G = PPA-agrammatic; PPA-L = PPA-logopenic; PPA-S = PPA-semantic; PPVT = Peabody Picture Vocabulary Test; V1 = visit 1; V2 = visit 2; WAB-AQ = Western Aphasia Battery–Aphasia Quotient.

Average percent correct (SD) for each neuropsychological measure is provided at baseline and 2-year follow-up by PPA subtype. Some patients were unable to complete testing for all measures at their 2-year follow-up visit because of disease severity. At V2, BNT data were not available for 2 patients with PPA-G and 1 patient with PPA-S; PPVT data were not available for 3 patients with PPA-S; grammatical production data were not available for 2 patients with PPA-L, 4 with PPA-G, and 2 with PPA-S; repetition data were not available for 1 patient with PPA-S.

[a] At V2, the average WAB-AQ score was significantly lower in the PPA-G group than in the PPA-L group.

[b] At V1 and V2, the average BNT and PPVT scores were significantly lower in the PPA-S group than in the PPA-L and PPA-G groups.

[c] At V1 and V2, average grammatical production scores were significantly lower in the PPA-G group than in the PPA-L and PPA-S groups.

[d] At V1, average repetition scores were significantly lower in the PPA-G group than in the PPA-S group.

[e] At V2, repetition scores were significantly lower in the PPA-G group than in the PPA-L and PPA-S groups.

PSTC—PPA-L: 8 small, 3 medium; PPA-G: 27 small, 11 medium; PPA-S: 16 small, 6 medium).

**Neuropsychological performance.** Average scores for language tests and severity are provided in table 2. Decline in scores was evident for all subjects, although there was variability at the individual level by test (figure e-1). ANOVAs were used to identify differences in performance by PPA subtype. Our measure of aphasia severity, the WAB-AQ, showed no differences at V1 among the subtypes, but at V2, the average WAB-AQ score was lower in the PPA-G than in the PPA-L group ($p = 0.009$). The average Boston Naming Test and Peabody Picture Vocabulary Test scores were lower in the PPA-S group than in the PPA-L and PPA-G groups at V1 and remained lower at V2 ($p \leq 0.010$, for each comparison). The average grammar production scores were lower in the PPA-G group than in the PPA-L and PPA-S groups at V1 and V2 ($p \leq 0.007$, for each comparison). The average repetition scores were lower in the PPA-G group than in the PPA-S group at V1, and at V2, the PPA-G group had lower scores than the PPA-L and PPA-S groups, which is consistent with previous findings.[8]

Given the relatively small number of subjects per subtype, statistical analyses were not performed to directly assess the relationship between atrophy and clinical decline within the PPA group or by subtype. This will be an important future direction.

**DISCUSSION** Quantitative atrophy measurements of 26 patients with PPA found significant deterioration within the language network for each of the 3 PPA subtypes over the course of 2 years. A primary finding was the presence of asymmetric progression of atrophy in the LH for each PPA subtype over the 2-year interval (figures 1 and 3), underscoring the neuroanatomical selectivity of neurodegenerative disease over time. The PPA-G group showed the greatest anatomical selectivity of progression. In fact, loss of cortical volume in the contralateral (right) hemisphere of this group during the 2-year interval was only detectable using an ROI approach. In the LH, incremental atrophy as a percentage of baseline over 2 years was greatest within, rather than outside of, the perisylvian cortex and surrounding temporal regions for all 3 subtypes (figure 3), which suggests that preferential neurodegeneration of the LH language network is a common denominator for all 3 subtypes, even as the disease progresses.

During the 2-year interval, a decline in all language scores was evident; however, the subtype-specific impairment of word comprehension in the PPA-S group vs grammatical processing in the PPA-G group was largely maintained. Individual performance patterns on neuropsychological tests were variable (figure e-1), making it challenging to provide clinical expectations at the individual level.

There have been few studies of progressive neuroanatomical change in PPA,[5,9,22–27] which have mainly focused on large-scale measurements of whole-brain volume, ventricular volume, cortical volume, or regional patterns of atrophy. The present study provides greater specificity by examining vertex-wise cortical patterns of atrophy over time as well as focal estimates of change within the PSTC region that encompass most of the key language network components. The vertex-wise analyses provide unbiased visual representations of the anatomical patterns of change across the cortex, which adds to the understanding of the natural progression of the disease by subtype. The ROI analyses provide robust

quantitative metrics for comparing progression among subtypes, which can be compared across studies. Investigators can select the method that is most suited to the purpose of a given study.

Power analyses from this study suggest that the cortex and PSTC ROI may provide more sensitive outcome measures than previously reported whole-brain and ventricular volume measures.[5] Thus, cortical ROI measures (especially the PSTC) may be useful for future clinical trials in PPA because they allow for smaller samples sizes to detect a significant effect.

There does not appear to be a simple relationship between initial volume and percent change over time. The PPA-S group had the smallest LH PSTC volume at baseline (table e-1); therefore, one might predict that they would also show a slower rate of progression over time, because they have less brain mass to lose. The data from this study did not support this hypothesis; instead, the percent change in volume of the LH PSTC region was larger in the PPA-S group compared with the PPA-G group (figure 3).

The findings from this study are consistent with prior longitudinal reports of atrophy[4,24] and neuropathologic findings in patients with PPA,[28,29] showing that peak atrophy, neuronal loss, and disease-specific proteinopathy primarily occur in the language-dominant (usually left) hemisphere. The reason(s) for this LH vulnerability in PPA is unclear and remains one of the most important questions in the field.

## AUTHOR CONTRIBUTIONS

Dr. Rogalski contributed to drafting/revising the manuscript for content, including medical writing for content, study concept or design, analysis or interpretation of data, obtaining funding, and statistical analysis. She has access to all the data and takes responsibility for the data, accuracy of the data analysis, and the conduct of the research. She has the right to publish any and all data, separate and apart from the guidance of any sponsor of the research. Dr. Cobia contributed to drafting/revising the manuscript for content, including medical writing for content, study concept or design, and analysis or interpretation of data. Mr. Martersteck contributed to analysis or interpretation of data. Dr. Rademaker contributed to analysis or interpretation of data and statistical analysis. Ms. Wieneke contributed to drafting/revising the manuscript for content, acquisition of the data, and study supervision and coordination. Dr. Weintraub contributed to drafting/revising the manuscript for content and obtaining funding. Dr. Mesulam contributed to drafting/revising the manuscript for content, including medical writing for content, study concept or design, analysis or interpretation of data, and obtaining funding.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## DISCLOSURE

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